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INDIAN JOURNAL
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Editor: U. B. NARAYANRAO

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The Role of The Laboratory in The Modern Diagnosis and Treatment of Venereal Diseases.

M. V. Krishna Murthi, B. A., M. B. B. S.
Lecturer in Venereology & Dermatology, Andhra Medical College and King George Hospital, Visakhapatnam.

The advent of Chemotherapy revolutionised the treatment of Venereal Diseases, but the impacts given by recent discoveries in the Antibiotic field has been tremendous. There have been great changes and simplification of treatment. The many uncertainties connected with the previous types of treatment and the numerous toxic reactions associated with them are to be met with no more.

The extensive use of antibiotics alone for the treatment of the different types of Venereal diseases had its own effect on the Venereologists too. They are finding that they are slowly losing their grip as a specialist, since treatment is getting simpler, non-toxic, nonhazardous and highly efficient.

Under these circumstances the proper diagnosis of Venereal Diseases has assumed greater importance. If the diagnosis is infallibly established, the treatment could be carried out in a systematic and routine manner, requiring less of specialised knowledge. With this in view, it is recognised that the laboratory should take over a new phase of diagnosing correctly the disease, assess the value of treatment undertaken, as well as show how the case is responding to the same. It could also help the clinician by choosing the correct drug of choice, assess the value of new drugs by undertaking sensitivity tests of the drugs on the organisms under study.

By the above it is not assumed that the Laboratory should take the role of the clinician. The clinician has his own place, but modern methods of diagnosis and help from the Laboratory could simplify and facilitate his work.

The laboratory should be well equipped and manned to do routine work and research, to improve its methods and tests and also work in liason with the clinic.

Taking some of the Venereal Diseases, Syphilis naturally leads the pageant. Serology in Syphilis had lagged behind a lot, but since World War II, tremendous strides have been taken. Lost ground has been retrieved by: (a) improvements in technique, (b) new tests and (c) standardisation of reagents.

The old Wasserman techniques have been improved upon to increase its sensitivity as well as its specificity. This has been achieved by (a) working on the theory of optimum proportions of Antigen in relation to the serum used. (PRICE) (b) by purification of the crude heart extract used in the Wasserman reaction-'Cardio-lipin' (PANGBORN) (c) improvements in technique by using the least amount of complement necessary to perform the reaction by proper titration methods, thus raising the sensitivity without the resultant loss in specificity (PRICE AND WILKINSON) (d) by improved methods of standardisation of antigens and other reagents used (PRICE).

NELSON in his Immobilisation technique of Treponema has gone a step further in trying to make this non-specific reaction into a specific one. The results are very promising, but at the present time it still requires highly specialised apparatus, reagents, methods and personnel.

Richardson's method of preservation of complement (which incidentally has not attained the popularity it so highly deserves) had solved yet another trouble for the serologist. A complement which keeps its complementary value at room temperature for more than a week, or at 4 Degrees C., indefinitely has made it possible to work out better titration methods, accurate calculation and the use of the least amount required without any qualms as to the ultimate result. The serologist's work is thus made more easy and less onerous.

Diagnosis of acquired syphilis could be made as under:—

(1) Dark field positive early cases	+	seropositive or not.
(2) Positive clinical findings	+	serologically positive.
(3) Suspicious or doubtful clinical findings.	+	serologically positive showing a rise in titre.
(4) Apparently no clinical signs.	+	serologically positive showing a rise in titre.
(5) Clinical findings	+	(A) Abnormal Biochemical reaction and cell count in C. S. F.
		(B) W. Reaction positive in C.S.F. and or blood.
(6) Apparently no clinical finding.	+	W. Reaction positive in C. S. F. with a rising titre and other pathological and biochemical findings.

In classication 3 and 4, the rising titre shown by the Q. W. R. over an appreciable period points in no uncertain manner towards the diagnosis of Syphilis.

It is as sumed that Wasserman Reaction which is in anamoly with the clinical condition is always repeated to overcome (a) mixing up of sera and improper labelling in the clinic. (b) technical false positive reactions in the laboratory and (c) any low wobbling biological false positives. It is essential that at least two tests, one complement binding and another precipitant should be done on each sera and at least one if not both should be of a quantitative character.

Technical false positives and biological false positives, are bound to occur even with the most improved methods of testing. The technical false positives occur due to multiplicity of procedure involved in the complement binding test but such errors generally do not leave the laboratory which undertakes more than one test as the anamoly in the readings are glaring in the final check up.

Biological False Positive:—Text books describe a host of diseases as giving B. F. P's, but in practice few are the culprits. These positives are generally evanescent or static in character and their titration index is low. They do not show a rise in index on repeated examinations. Further evaluatiqns of such sera are done with the help of Cold agglutinin reactions. Paul Bunnel and other absorption tests are too complicated to discuss here. The Universal reaction described by Kahn and coworkers in evaluation of such cases deserve mentioning here.

Certain of the precipitant reactions like Price's Precipitant reaction and Meiniche are claimed to give very specific results. From experience I have found that both these tests do live up to their claims (see alse PRICE Lancet Jan. 1950).

The false positives met with in yaws cannot be evalued as the causative organism of the disease is allied to syphilis.

The Wassermann and the precipitant reactions for Syphilis done on a quantitative basis helps the clinician both in the diagnosis and treatment progress of the case. A screen W. R. gives no indication whatever till it goes below the serological threshold producing a negative result. A serological relapse precedes a clinical relapse, assuring early appraisal and treatment of the condition. The wobbling type of W. Rs and the fluttering types are not discussed here, but the fact remains that the modern methods of doing W. R. reactions are more specific and sensitive (KBAG).

The reporting of W. Reaction as strong positive, positive, doubtful carry little meaning and has no bearing on its quantitative character as all serologists knew (MOORE). This reaction depends on the complement reading as

well as a high degree of constancy in the four other main componants of the reaction. These gradations are purely arbitrary and individualistic. A truer picture of the W. reactions are given at the STATEN Serum Institute—Copenhagen by giving a haemolysis curve even in the Q estimation. But an easier and accurate method of sending reports is expressed in doubling serum dilutions and the last tube showing complete fixation is taken as the final titre.

Few typical serological reactions are appended below as Fig. 1, 2 and 3.

Fig. 1.

Showing the serological reactions after treatment of a case of secondary syphilis. There may be an initial rise even after treatment, followed by either a sudden drop, medium or slow reversal to the negative phase. This state can only be made intelligent by Q reactions.

Fig. 2.

A case of Sii, treatment instituted middle of 2nd month showed good serological response up to 4th month and started serorelapse, but showed clinical relapse a month later.

Fig. 3.

A case of Sii showed a good response after treatment but kept positive at a low level. Later it relapsed. A C. S. F. finding at that time showed mild pathological changes. This case of serorelapse with early neurosyphilis could not have been diagnosed by screen test of W. R. till perhaps a routine L. P. was done or clinical manifestation of neurosyphilis was evident.

Gonorrhoea:—is generally diagnosed on finding in a urethral discharge evident or otherwise, gram negative diplococci, intracellular, morphologically similar to Neisseria Gonococci. Quite a few other organisms simulate the above condition. The Neisserian family between themselves are difficulat to identify microscopically. Coliform bacilli sometimes take on coccoid forms and are found intracellular and are mistaken for gonococci. The only may to avoid the above is by culturing the gonococci which is easily done either in Mcleod's chocolate agar medium, plain or enriched, or Hydrocele agar or Ascitic agar medium. They could be easily identified by their colonial appearance, the oxidase reaction, the staining characteristics and biochemical reactions. These are simple and not time consuming and could be done as a routine, thus placing above all doubt the nature of organism under study. This is daily done on a very large scale at the Serum Institute, Copenhagen, quite successfully.

It is also well known that in the smear from the female genital tract gonococci are very difficult to identify due to the other flora present like Gram negative cocobacilli. Further in the p. h. prevalent in the vaginal tract, some gram positive organisms do lose their gram positive character. Wilkinson

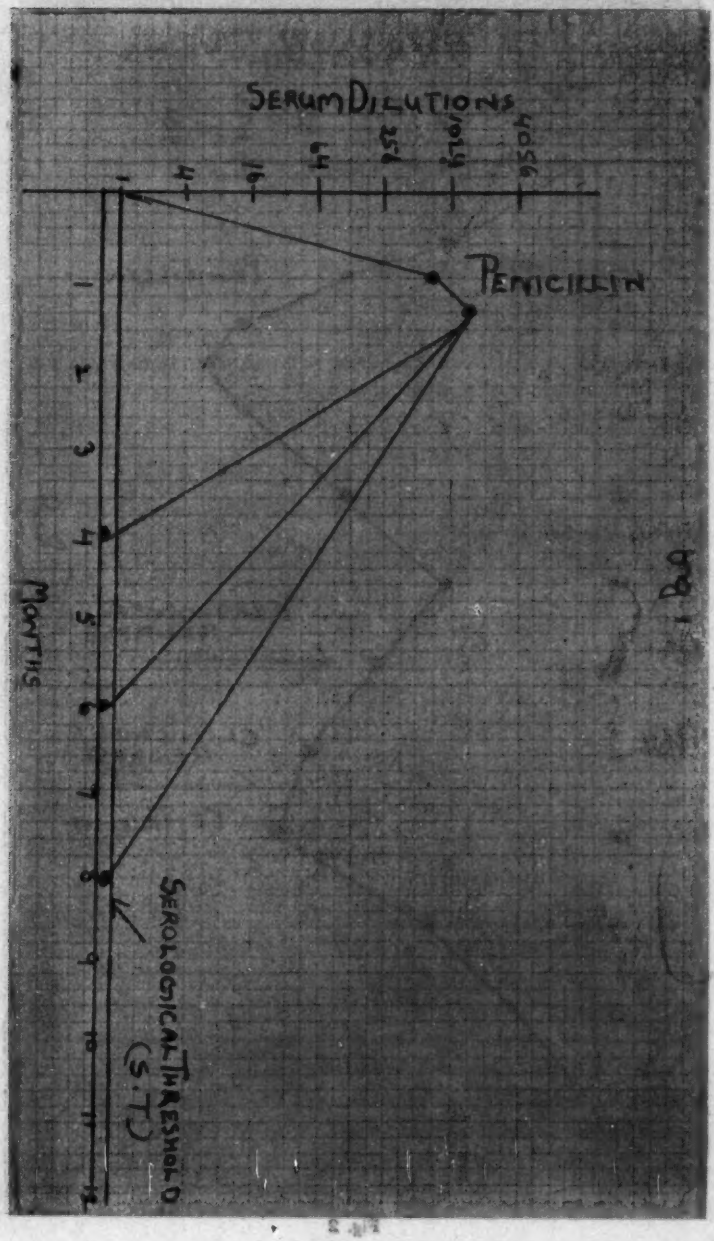
SERUM DILUTIONS
1/4
1/8
1/16
1/32
1/64
1/128
PENICILLIN
MONTHS
SEROLOGICAL THRESHOLD
(S.T.)

Fig. 1

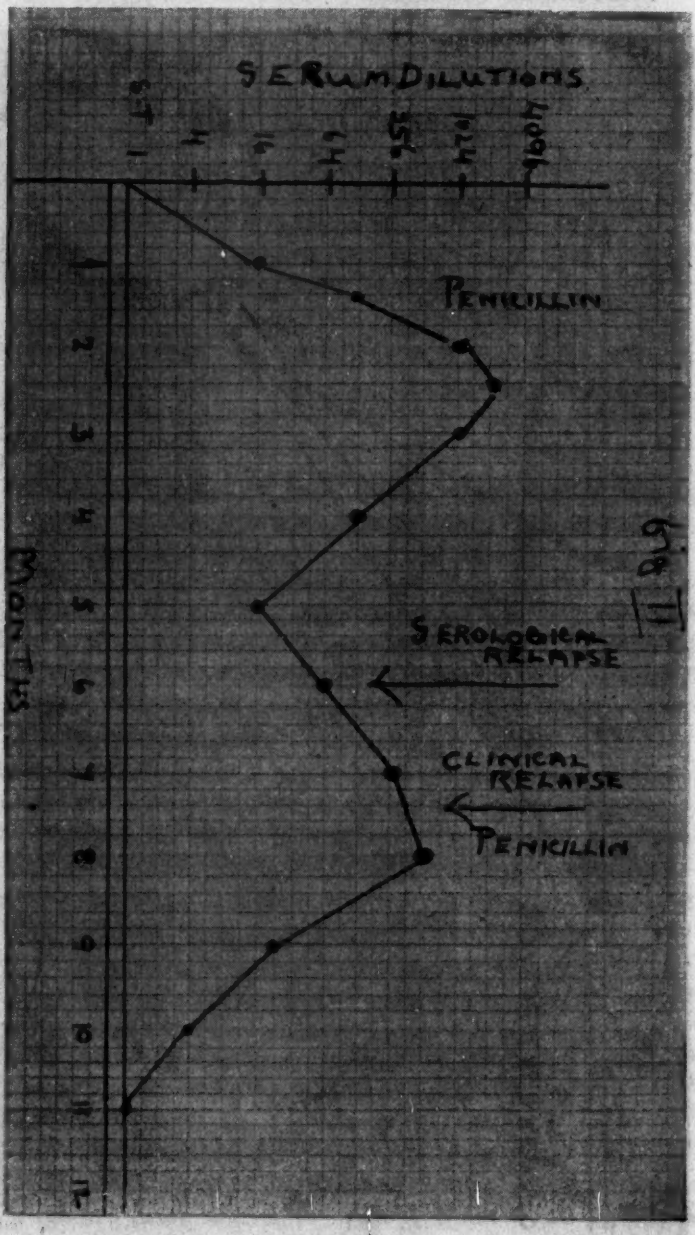
SERUM DILUTIONS
PENICILLIN
SEROLOGICAL RELAPSE
CLINICAL RELAPSE
PENICILLIN
WEEKS
11-8-49

Fig. 2

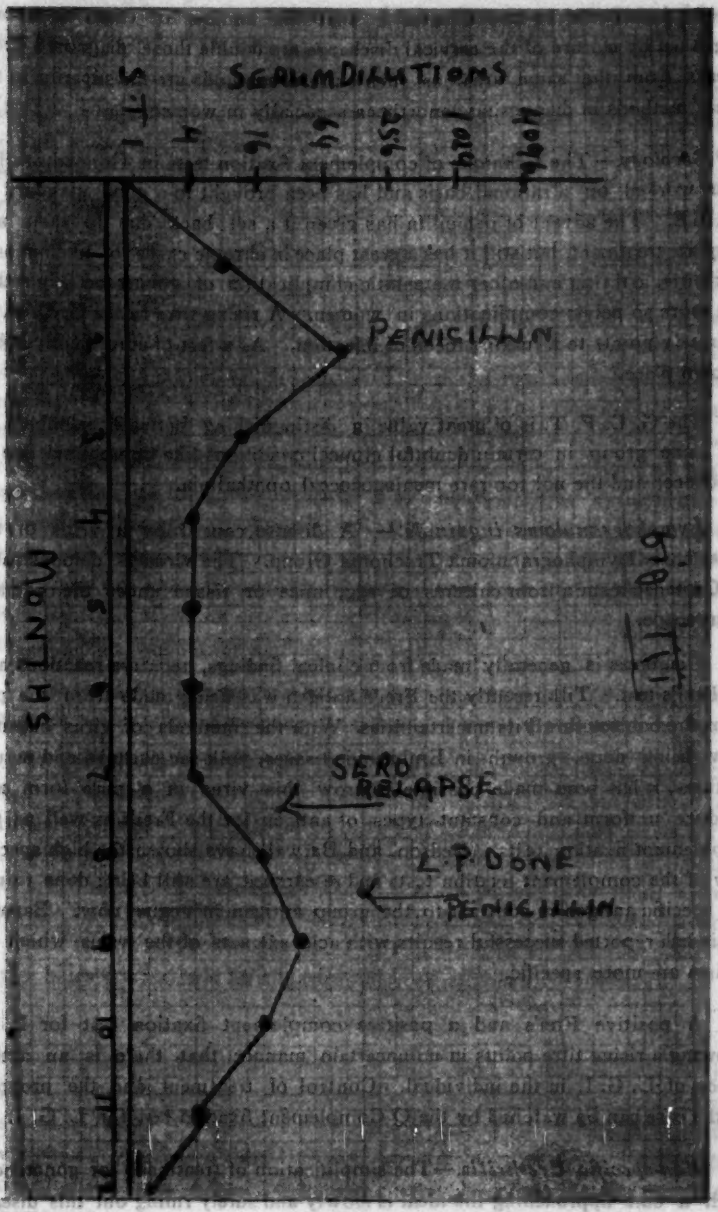
SERUM DILUTIONS
1
4
16
64
256
1024
4096
PENICILLIN
SHOWN
SERO RELAPSE
L.P. DONE
PENICILLIN

Fig.

(1940) has come to the conclusion that the number of cases in women diagnosed by culture of the cervical discharge are double those diagnosed from smears from the same area, as such cultural methods are far superior to the smear methods in diagnosing gonorrhoea especially in women.

Serology:—The technique of complement fixation tests in Gonorrhoea has been worked on a rational basis and has been brought to a good standard by PRICE. The advent of penicillin has given it a set back due to early and adequate treatment, but still it has a great place in chronic cases of undiagnosed urethritis, arthritis and other metastatic complication of gonorrhoeal infection and more so pelvic complications in women. A rising titre in the G. C. F. T. definitely points to a lurking focus of infection. As a test of cure finally it has its own place.

The G. C. F. T. is of great value in distinguishing between members of the same group in certain doubtful clinical conditions like ophthalmia due to gonococci and the not too rare meningococcal ophthalmia.

Lymphogranuloma inguinale:— A disease caused by a virus of the Psittacosis Lymphogranuloma Trachoma Group. The virus is demonstrated by Castened's stain from cultures of egg, mice or tissue under the ordinary microscope.

Diagnosis is generally made from clinical findings, negative reactions and by Frei's test. Till recently the Frei's antigen was being made from the pus from the bubo with all its uncertainities. With the methods of virus cultures now being done, growth in Embryonic tissues, yolk sac cultures and mouse cultures, it has been made possible to grow this virus in a pure form and produce uniform and constant types of antigen for the Frei's as well as the complement fixation tests. Bedson and Barwall have shown the high specificity of the complement fixation tests and researches are still being done to use the specific antigen in contrast to the group antigen in vogue now. Barwell again has reported successful results with acid extracts of the virus which he claims are more specific.

A positive Frei's and a positive complement fixation test for L. G. showing a rising titre points in no uncertain manner that there is an active lesion of L. G. I. in the individual. Control of treatment and the progress of the case can be watched by the Q Complement fixation test for L. G. I.

Non-specific Urethritis.—The simplification of treatment for gonorrhoea with a cure approaching the ideal is slowly and surely ruling out this disease as a major problem. But as the gonococci is receding from the stage, the number of nonspecific urethritis with a completely abacterial urethral discharge

is assuming greater importance. Reiter's syndrome complex or the simple abacterial urethritis has become the head-ache of the venereologist due to its refractive nature to treatment.

Harkness and coworkers have suggested that it is due to some pleuropneumonia like organism and a virus theory was also put forward, on the assumption of the presence of inclusion bodies in the urethral mucosal scrapings of affected persons. The virul theory has not been substantiated since it has failed to produce anything after repeated passages in the chick embryo and mice.

FREUNDT of Copenhagen has grown from urethral scrapings pleuropneumonia like organisms in special media, containing penicillin and thallic acid but he is of the opinion that they are not pathogenic. Others were of the opinion that this urethritis is caused by L. Organisms. Salaman expounded on the same and suggested that the L. Organisms seen is some phase in the gonococci. FREUNDT of Copenhagen working on Bacillus Proteus in graded penicillinised medium has been able to convert the bacillary form into L. forms and reversing the process back into the bacillary form. This has also been proved by Orsokov and Dienes. The above work of Freundt sets one thinking whether, after all, Salaman was correct in his suggestion of environment and growth factors producing a life cycle for the gonococci. Researches on these lines are going on and it is hoped that very soon the clinician would be presented with the nature of the causative organism of this disease as well as the drug to which they are susceptible.

Venereal Granuloma:—is being treated successfully with streptomycin, but researches on this disease are too few and the field is still open.

In addition to the above routine investigations and research which a laboratory undertakes to help the clinician in his diagnosis and follow up of various diseases, it can successfully select the drug of choice to combat any particular organism, by finding out its susceptibility to the same, as well as estimate the amount of the drug circulating in the various body fluids after its administration to indicate whether sufficient antibiotic level is being kept up or not. This invariably makes the clinician's work easier and happier. The future holds a great field for the pathologist to explore and rationalise.

Acknowledgement

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Problems in the Therapy of early Syphilis

By

Charles R. Rein, M. D.

Assistant Professor of Dermatology and Syphilology, New York University, Bellevue Medical Centre, New York N. Y.

There has been a marked reduction in the incidence of reported early syphilis in the United States. This marked reduction is probably due to two main factors; the introduction of penicillin therapy and the subsequent development of adequate and effective ambulatory schedules that can be easily employed by physicians.

A voluminous amount of data on the efficacy of penicillin therapy in early syphilis has been recorded since the first report in 1943 by Mahoney. As with many new therapeutic agents, some of the earlier reports appeared inconclusive and were interpreted as unsatisfactory. Why so? Where were the errors in the interpretation of results? The following discussion may explain some of these discrepancies:

Inadequate Dosage

It is now an accepted fact by most investigators that there is a ***minimal total dosage*** of penicillin that must be administered if one is to obtain satisfactory results. Amounts below this minimal total dosage will result in high failure rates.

Inadequate Duration of Therapy

It has been shown that the time-dosage relationship is most important and that there is a minimal time during which penicillin can be effectively

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The Finnish and French Health Administrations organized, in co—operation with the World Health Organization, international symposia on syphilis, in order to allow a wide exchange of scientific information with outstanding American workers in this field.

It is well known that for some time different schools of thought have governed the outlook in syphilotherapy and serodiagnosis of syphilis in different parts of the world. The uneven production, distribution and availability of penicillin and cardiolipin antigens with resulting rapid accumulation of experience in some areas and slower in others, represent only part of the picture. More direct contact between outstanding experts with varied and varying experience in venereal-disease control would make for a more effective exchange of scientific information. To this end the World Health Organization has taken the initiative to encourage informal round-table discussions in Europe in 1950 and 1951, and the opportunity to bring together experts in the field of syphilis from 20 countries was provided through the International Symposia in Helsinki and Paris from 25 th Sept. to 7 th Oct. 1950. The symposia consisted of four Sections: Early Syphilis: Prenatal and Infantile Syphilis: Neurosyphilis: Serology in Syphilis.

Abstracts of the papers will be published in the Journal

—Ed. I. J. V. D.

administered. Keeping the total dosage constant, the longer the period taken to administer the penicillin (within certain limits) the more effective was the therapy. The likelihood of curing at least 90% of all patients with early syphilis with any penicillin preparation which will maintain a serum concentration above 0·03 units per cc. for a period of 72 to 96 hours has been suggested by Mahoney on the basis of analysis of the data of his group since the beginning of his early schedules. Unless the duration of therapy is adequate, there will be a relatively high incidence of failures. Eagle has found that the Treponema pallidum is the most sensitive of all the many different pathogenic bacteria which he has studied and that low concentrations of penicillin are profoundly lethal. The killing time, however, is longer for Treponema pallidum than for other pathogens investigated, indicating again the necessity of maintaining adequate levels of penicillin in the serum and tissues at the site of infection for a sufficient period of time.

Inadequate Knowledge of The Chemistry of Penicillin

When new techniques were developed for the production of penicillin on a large commercial scale, the chemical character of the antibiotic began to change. There were variations in the components (penicillin G, F, X, and K) in different commercial lots. It was reported that penicillin K, unlike penicillin G, was rapidly destroyed or inactivated in the body, and thus was relatively ineffective against the Treponema pallidum. It is quite possible, therefore, that the use of penicillin K during this period might have been responsible for reported failures in syphilo-therapy. As the situation was corrected and the newer preparations consisted predominantly of penicillin G improved therapeutic results were reported. When the total dosage was raised to 2·4 million units, and the penicillin preparations improved, the percentage of satisfactory results was markedly improved.

When one realizes that the serologic response in high titered early syphilis may be slow; that the serologic reversal in old latent syphilis or in late congenital syphilis is not to be expected even within 5 years after treatment, and that the persistence of positive serologic tests for syphilis does not necessarily indicate the persistence of infection, it will then be possible to appraise more accurately and intelligently the results of penicillin therapy for syphilis. Furthermore, unless quantitative serologic tests are performed at rather frequent and regular intervals on patients with high titered reactions, it may not be possible to determine whether there is a satisfactory trend following therapy.

The studies were directed along the following lines.

Development of Absorption Delaying Methods

Recently Bristol Laboratories described a combination containing procaine penicillin (small-particle size) in peanut oil jelled with 2% aluminum

monostearate. A single injection of one cubic centimeter (300,000 units) maintained a serum concentration of penicillin above 0.03 units per cubic centimeter for 96 hours in approximately 90% of the 173 patients studied. In a subsequent report Kitchen and his associates were able to show that the daily injection of 1 cubic centimeter (300.000 units) daily for 15 days resulted in a progressive serum accumulation of penicilln. This began with a serum concentration of 0.1 unit per cubic centimeter, 24 hours following the first injection, attaining an average of about 0.4 unit per cubic centimeter by the eighth day, and maintaining this same high level thereafter. A similar phenomenon resulted from the injection of the same amount of penicillin at 48 hour intervals, but the accumulation rate was slower and the serum concentration level lower at the end of the eighth day, being approximately 0.2 units per cubic centimeter. In the same publication we also reported serum concentrations of penicillin following the single injection of this penicillin preparation as follows:

Schedule 1. 1.2 million units (4 cubic centimeters) one depot.
Schedule 2. 2.4 million units (8 cubic centimeters) one depot.
Schedule 3. 2.4 million nnits (4 cubic contimeters) in each of two depots.

Schedule number 1 produced a peak level of approximately 0.5 units per cubic centimeter in one hour and remained above 0.03 units per cubic centimeter for 6 to 8 days. Schedules 2 and 3 produced serum levels of approximately identical magnitude. The one hour peak concentration for these was approximately 1 unit per cubic centimeter. A gradual decline in the level which fell below 0.03 units per cubic centimeter occurred in about 8 to 10 days in most patients. With this information, our group at New York University-Bellevue Medical Centre initiated four schedules of treatment for early syphilis.

The ultimate objective in the treatment of syphilis from the public health standpoint is to effect eradication of this diseese. This will eventually be accomplished by methods which will actually "cure" or render non-infectious patients in the early stages. We are, therefore, concerned in our work and in this study, with early syphilis and have chosen subjects in the primary and secondary stage of the disease for this evaluation. This report is not concerned with speculations as to the therapeutic management and outcome with patients with old syphilis, where irreversible, anatomical or serologic changes may have occurred. These studies were started in May of 1948. Since they were the first patients to be treated on such brief schedules with the penicillin preparations, and since we did not wish the possiblity of a high failure and relapse rate, we did not administer less than a single injection of 1.2 million units in any schedule. Simultaneously with the treatment schedules, sera were assayed for the concentration of penicillin produced and maintained by the

injections of these varying amounts of this product. The four treatment schedules were as follows;

Schedule 1. A single injection of 4 ccs (1. 2 million units).

Schedule 2. A single injection of 8 ccs (2. 4 million units).

Schedule 3. A single injection of 4 ccs once a week for two weeks (2.4 million units).

Schedule 4. A single injection of 4 ccs once a week for four we ks (4.8 million units).

At this time, I shall only report on the results obtained in those patients who received single injections of 4 or 8 ccs of procaine penicillin in oil and aluminium monostearate (schedules 1 and 2).* Since there was no appreciable difference noted in the results obtained with these single injection schedules they will be considered as one group. Seventy-one patients had been followed for from 6 to 20 months at the time of this report (April 1950). Twenty-three received 2.4 million units and 48 received 1.2 million units. Of the 71 patients, 6 were treated for seronegative primary syphilis, 16 for seropositive primary syphilis, 44 for secondary syphilis and 5 for darkfield positive syphilis caused by relapse or reinfections following previous treatment for early syphilis with other schedules. When last examined, 60 (84. 5 per cent) had negative serologic reactions with the complement-fixation and kahn tests, 7 (9.8 per cent) had shown reductions in serologic titers and 4 (5.6 per cent) were retreated for the following reasons: 1 was reinfected; 2 relapsed or were reinfected; I had a Kahn titer of 16 units one year following completion of therapy.

Although the date presented in this report are inadequate for valid conclusions at this time, it appears that there is no advantage in weekly injections of procaine penicillin G in oil and aluminium monostearate in the treatment of early syphilis.

The second study upon which I wish to report briefly is that of Doctors Loveman, Buschmeyer, Zaug, and Fliegelman carried out at the University of Louisville.

The same penicillin preparation was used in their study as in the study reported from the New York University-Belevue Medical Centre group. A total of 102 patients were selected for this study, of which 20 were in the seronegative primary stage, 29 were in the seropositive primary stage, and 53 had secondary syphilis. Each patient was subjected to a clinical and serologic examination prior to therapy, at weekly intervals while under treatment, and at monthly intervals thereafter for one year. Spinal fluid examinations were made from

* Grateful acknowledgment is made to Bristol Laboratories, Inc., Syracuse, NY, for making this work possible by a grant-in-aid plus their product, Flo-Cillin "96".

the 6 to 12 months following completion of therapy. Each patient received one injection of 1 cc (300,000 units) of procaine penicillin G in oil and aluminum monostearate once a week for 4 weeks (for a total of 1.2 million units). These patients were followed for from 2 to 18 months. Of these there were 42 white and 58 coloured patients. Fifty were males and 52 were females.

It will be noted that 82 patients had attained serologic cure and 7, serologic improvement. In this study, 13 patients were classified as failures, of which 5 were serologic relapses, 6 were clinical relapses, and 2 reinfections.

These results would seem to indicate that the results obtained at the New York University–Bellevue Medical Centre with a single injection of 4 ccs were somewhat better.

The third study is that of Wright, Nicholson and Arnold from the Venereal Disease Research Laboratory. They believed that a single injection treament of syphilis would be possible for the following reasons:

1. A 72 hours treatment schedule 200,000 units of crystalline sodium G every 2 hours for 36 doses gave excellent results as judged by more than 2 years of observation.

2. As little as 300,000 units of microcrystalline procaine penicillin with 2% aluminium monostearate would produce a detectable level of penicillin in the blood for 72 hours in 97% of the patients tested.

The same type of penicillin preparation was used by this group as in the two previous studies discussed in this report. They decided to use a single injection of 300,000 units because other investigators were using single injections of larger doses. Furthermore, they felt it would be worth while to ascertain whether the low dosage would suffice.

This study was comprised of 99 patients with early syphilis, who were observed from 1 to 16 months. At 9 months, a follow-up on 50% of the patients revealed that 6 were retreated for serologic relapse and 5 for clinical relapse, with a cumulative failure rate of 15·3 per cent. It was of special interest, however, that 66% had attained and maintained seronegativity. This is obviously not an optimal schedule of treatment. In their series of 386 patients, who received 200,000 units of aqueous penicillin G every two hours for 36 doses, the cumulative failure rate at the end 9 months was only 1·1 per cent. Even after 2 years, the cumulative retreatment rate was only 6·3 per cent and most of them were considered to be reinfection. The investigators conclude, therefore, that:

1. Maintenance of a detectable serum penicillin level for 72 hours is not a guarantee of cure in early syphilis.
2. A single injection of 300,000 units of propenalate does not provide a sufficiently high cure rate in early syphilis to be used in this country.

The fourth and last report is that of Doctor Chargin, Sobel and Rosenthal. This group had already reported on two other series of patients at the New York City Board of Health. The first series of patients received daily injections of 300,000 units of penicillin in peanut oil and beeswax for 16 days for a total of 4·8 million units. The second series received similar injections of the same type of penicillin preparation twice a week for a total of 8 weeks for a similar total of 4·8 million units. The satisfactory results in these two series were almost identical with a relapse rate of about 4%. In considering means of improving the therapeutic results and, if possible, to reduce this relapse rate, they instituted therapy in a third series of patients which had for its object, the answer to the question: "does combined treatment with penicillin, mapharsen and bismuth yield better results in early syphilis than penicillin given alone"?. The study was carried out in the clinics of the Department of Health of New York City. Of 540 initially admitted unselected cases of early syphilis, 470 completed the full or nearly full course of treatment. The study covers a period of a little more than two years. The treatment consisted of the administration of penicillin G in oil and beeswax or of procaine penicillin in aluminium monostearate, given daily for 10 consecutive days (omitting Sundays): the total therefore, was 6,000,000 units. By far the majority of patients received the procaine penicillin. The penicillin therapy was followed by semi-weekly intravenous injections of marpharsen for 10 successive weeks (dose 0.045 to 0.06) and this in turn by 1 to 1-1/2 ccs of a 10% suspension of bismuth in oil for 10 weeks. In some the marpharsen and bismuth were given concurrently. The entire treatment, therefore, covered a period of from 10 to 16 weeks. In their summary the authors state the apriori expectation of a higher "cure" rate with combined therapy has not been realized since the satisfactory outcome in the their studies are about the same. So far as the effect upon the clinical manifestations is concerned, all there schedules, of course, furnish highly satisfactory results. The outstanding difference was the low retreatment rate with a combined schedule (approximately 1 per cent as compared to the 3.9 per cent in the 16 day plan).

Any therapeutic regime designed with the view ultimately to eradicate syphilis must be primarily concerned with actually curing or rendering non-infectious the disease in its early stages. Accumulated experiences definitely indicate that this can be accomplished with penicillin alone and that the adjuvant use of heavy metals or fever therapy does not appreciably increase the cure and improvement rate of the disease.

The question of what disposition to make of a patient in whom penicillin or any other treatment has failed deserves special attention. The report of Thomas and Landy from Bellevue Hospital discloses that more than 4,000 patients have received various forms of therapy. Of these, 689 have been

retreated one or more times with penicillin, because of relapse or reinfection. Of these, 409 have been followed upon completion of the last treatment for 12 to 53 months. Three hundred and thirty-three (81.4) were seronegative, 67 (16.4) had positive Kahn tests in dilutions of 1:2 or less, and 9 (2.2) had persistent Kahn titers in dilutions of 1:4 Mahoney's results show that approximately 80% of all failures may be successfully retreated with penicillin. So far, there has been no proven evidence of a true resistance to penicillin therapy. Thus, in failure, retreatment with penicillin is indicated rather than subjecting the patient to years of administration of toxic chemotherapy with arsenic and bismuth.

I should like to suggest the following schedule for the teatment of all patients with early syphilis. On the first day, administer one injection of 4 cc. of procaine penicillin in oil and aluminium monostearate (1·2 million units), then, if possible, arrange to give that patient one injection of 1 cc. once a day for 6 additional days or 600,000 twice a week for three weeks. The advantage of this plan of therapy is that an adequate dosage of penicillin is administered on the first day of treatment. Should that patient fail to return for additional therapy, the physician can have the assurance that he has better than a 90 per cent chance of rendering that patient non-infectious and "curing" his infection.

By-Effects of Penicillin Therapy

A great deal has been reported on the subject of reactivity to penicillin when administered by different routes. Most workers agree that approximately 5 per cent of all the patients receiving the soluble penicillin salts (sodium, potassium or calcium) by injection will manifest some degree of skin response in one form or another. This was viewed early as a complication of great importance, since drug sensitivity in the past had proved to be most bothersome and often precluded the administration of an indicated medicament. Thomas reporting on the sensitivity response in 10,000 patients treated with penicillin for syphilis, analyzed the severity of the situation. In most instances skin eruptions were not considered sufficiently important to withhold penicillin by injection. It is now well recognized that the urticaria appearing in the average patient sensitive to the antibiotic may disappear in a few days even on continuation of treatment. During this time large doses of antibistaminic drugs adminisrered by mouth may help considerably.

In Dr. Chargin's last report he writes, "during the first few months of our study, POB (penicillin in oil and beeswax) of the fluid variety was employed in treatment, and during this period approximately 10% of the patients showed reactions. Later, with a change to procaine penicillin there was a remarkable drop in reaction to about 1%. The type of penicillin reactions observed were chiefly urticarial, immediate or delayed contact type of dermatitis

and activation of fungus sites. In none was it found necessary, except for a short period, to interrupt treatment". Our own obeservations to date following the intramuscular injections of procaine penicillin in oil and aluminium monostearate in over 3,000 patients indicated that the sensitivity rate is definitely less (approximately 1%) with this product than with the older penicillin used in the past. Severe reactions to penicillin can occur and in 1947, Dr. Sawicky and I reported two such patients. The following classification of common reactions to penicilin was previously reported by Romansky.

A. Toxic Reactions,
   1. Intrathecal penicillin reaction'
   2. Herxheimer reaction—Not peculiar to penicillin, but common to all potent spirocheticides and antibacterial agents.
   3. Therapeutic paradox.

B. Allergic Reactions.
   1. Pruritus, urticaria, angioneurotic edema, asthma, serum-sickness-like reaction and anaphylaxis-like reaction (immediate or delayed).
   2. Erythematovesicular desquamating type.
   3. Contact dermatitis type.
   4. Experimental.
      (a) Arthus type.
      (b) tuberculin type.
      (c) anaphylaxis.
      (d) photosensitization (?)

In a cursory examination of the recent literature, I was able to find reports of 7 fatalities following penicillin therapy. Of these, 3 are questionable. In 1, a febrile course terminated fatally 9 days after an abdominal operation for carcinoma. It is not possible in this case to exclude carcinoma as a cause of death. The second patient was suffering from a streptococcal septicemia which may have been the cause of death instead of the penicillin reaction. The third patient was a 53 year old man treated for a furuncle on the neck with two daily intramuscular injections of penicillin in an absorption delaying vehicle. Four days later he developed a pruritic rash which became generalized and began to exfoliate. Anuria, dyspnea, nausea and vomiting developed. He died approximately 15 days later. The patient had a history of nephritis and post-mortem examination revealed that death was due to a chronic glomerulonephritis and exfoliative dermatits. When one realizes that millions of patients have received penicillin therapy, and yet there are so few reported fatalities, penicillin can be considered an extremely safe form of treatment for syphilis.

Conclusion

Hitherto, confusion has existed regarding the proper place of penicillin in the treatment of syphilis. The possible reasons for this misinterpretation of the problems are discussed. It we are to judge by the majority of reports in the literature to date, penicillin alone is the drug of choice in the therapy of early syphilis and combined therapy with arsenic and bismuth appears to be of doubtful value. There is complete agreement that the administration of penicillin alone in early syphilis results in: (1) the rapid disappearance of Treponema pallida from lesions; (2) the rapid healing of skin and mucous membrane lesions; (3) the reversal to seronegativity of serologic tests in more than 90 per cent of the patients during the first two years following therapy; and (4) the completion of therapy on an ambulatory basis in the majority of patients. Another tremendous advantage of penicillin therapy is its safety, since arsenical therapy by any schedule carries a definite irreducible risk of reaction and even death. To place into effect the best ambulatory schedule for the treatment of early syphilis will require the close collaboration of investigative clinicians throughout the world.

International meetings of this type, which have been made possible by the World Health Organization where therapeutic problems can be fully discussed, will help tremendously in solving this problem.

Procain Penicillin in Oil with Aluminium Monostearate (P.A.M.)

IN THE TREATMENT OF

Early Infectious Syphilis, Prenatal and Infantile Syphilis

By

F. W. Reynolds, M. D., M. P. H.

and

Th. Guthe, M. D., M. P. H.

World Health Organization, Geneva, Switzerland

It took several years following the introduction of arsenicals and bismuth in syphilotherapy before a fairly precise evaluation of the outcome of the disease with this form of treatment became available. The reason for this was partly that metalchemotherapy was of long duration—several months—and many patients were lost before completion of treatment and partly that still further patients were lost from follow-up observation when treatment had been completed. A sufficiently large material on which to base bio-statistically valid conclusions was therefore not easily accumulated. The Health Organization of the League of Nations took up this question in the early 30's through the International Study Commission on Syphilis and Cognate Subjects, ably

chaired by Professor John Stokes of U. S. A. and Professor Martenstein of Germany. The study included some 80,000 clinical records from five countries. On the basis of the findings of the Commission standardized treatment schedules with metalchemotherapy were subsequently established in most countries of the world (1930–1939).

The findings of the Commission showed that in early infectious syphilis, approximately 95 per cent of patients with seronegative primary syphilis, 90 per cent with seropositive primary disease and 85 percent of secondary syphilis were " cured " when adequate treatment was given. Cure was defined as clinical and serological negativity and normal spinal fluid findings by the end of a two year observation period. It was established that the earlier the diagnosis was made, the more effective was the therapy and the more favorable the outcome of the disease.

More than eight years have now elapsed since Mahoney and his co-workers (1) made the first preliminary report of the effectiveness of penicillin in the treatment of syphilis. In this comparatively brief period of time an enormous information has been accumulated regarding the usefulness of this form of therapy, and it has become increasingly clear that the availability of penicillin has revolutionized the treatment not only of the many manifestations of syphilis, but also of the other diseases of treponemal origin, yaws (2), bejel (3) and pinta (4).

The preliminary assessment of the results of penicillin therapy in early infectious syphilis indicated a higher proportion of unfavorable results than is now to be the case. The improvement in the penicillin itself by the elimination of the relatively inactive K fraction present in the first amorphous, yellow penicillin preparations; the subsequent development of Crystalline Penicillin G (5), free from impurities and inactive elements; the recognition that foreshortened schedules of therapy not infrequently increase the number of reinfections, which represents therapeutic success rather than failure in the individual case (6); the growing appreciation that more than a few of the earlier cases were needlessly retreated–and therefore considered to be " failures "–on the basis of inadequate serologic grounds (7), all suggest that penicillin is therapeutically more effective than was at first suggested (Fig. I).

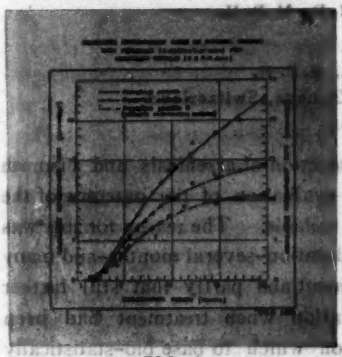

FIG. I

In order to establish the most conservative basis for evaluation Fig. 1 has been based on large series of cases of secondary syphilis only. The improvement

in the results with the introduction of crystalline penicillin G is readily appreciated from the graph. Probable reinfections have been excluded in the lower curve, and it will be seen that the retreatment rate is approximately 11 percent in secondary syphilis treated with a minimum of 2.4 million units of crystalline Penicillin G and followed for two years.

Because of its rapid excretion, penicillin therapy formerly required hospitalisation and repeated injections at frequent intervals. With the development of absorption delaying preparations, however, ambulatory therapy became feasible. Currently in widest use is a suspension of the slowly absorbed procaine salt of crystalline penicillin G in oil gelled with two percent aluminium monostearate. This type of preparation is internationally designed as *P. A. M.* With this type of preparation it has been repeatedly demonstrated that therapeutically effective serum concentrations of penicillin can be maintained for 2–3 days following a single injection of 300,000 units, and 4–5 days or more following 600,000 units. Following 1.2 and 2.4 million units effective concentrations in the serum can be maintained for approximately 8 and 10 days respectively. In surgical technic as much as 6–10 million units of P. A. M. can be deposited intramuscularly in one procedure, maintaining of effective serum level for some three weeks. Penicillin crystals of approximately 5 microns in diameter appear to give serum concentrations of longer duration than do preparations of smaller particle size and 80% of the particles in the preparation should be 5 microns or less.

It appears that by the end of a two year observation period the overall cure rate in early infectious syphilis is approximately 90 percent with penicillin action over 8–10 days (8, 9, 10). The effectiveness is greatest in *primary seronegative syphilis*, approximately 95%, somewhat less in *seropositive primary disease*, namely 90%, and again somewhat less in *secondary syphilis* (approximately 87%), the criteria for " cure " having been defined previously in this article. These cure rates would be slightly higher if reinfections are excluded. In order to achieve this several treatment schedules can be used, *the essential feature being that an adequate blood level be maintained for a sufficiently long time, and not whether a " one-shot or a few-shot " treatment schedule was employed.* A schedule should be selected which will be convenient to the patient as well as to the physician, and attention should be paid to the possibility of the patient disappearing from the treatment visits prescribed. Certain investigators therefore prefer to apply on the first day of treatment 1.2 million units of penicillin, with subsequent injections on the 5 and 10th day of 600,000 units of P. A. M. for a total minimum of 2.4 million units of P. A. M. Some prefer to continue treatment for a total of 4.8 million units of P. A. M. although there is at present no clear cut evidence that the results improve significantly beyond 2.4 million units, if an adequate regimen has been prescribed and followed.

Metalchemotherapy, adjunctive to penicillin

The rationale of giving adjunctive therapy centers around the observation of Eagle and his co-workers (11) and Magnuson and Roseman (12) of a synergistic action between penicillin and the heavy metals. What is seldom realized however is that the synergism that has been described in experimental animals by these workers is between sub-curative amounts of the two forms of therapy and that there is little evidence of synergism when adequate amounts of either preparations are used. The american clinical experience indicates clearly that when only a few arsenic and bismuth injections are given *concomitantly* with penicillin there is no evidence of increased therapeutic effectiveness.

Penicillin and Consolidation with Metal-chemotherapy.

There is also the question of the advisability of "consolidating" a preliminary course of penicillin with metal-chemotherapy administered over a longer period of time. Prolonged consolidation with bismuth following initial penicillin treatment is preferred by Gougerot and Degos (13) in France and by others. Th se investigators at the present time are also carrying out studies with P. A. M. alone, as are other French outstanding syphilologists (Joulia). In the Scandinavian and other European countries including United Kingdom penicillin plus metal-chemotherapy was until recently the accepted therapeutic regime, however several major clinics in European countries are now dropping the metaltherapy. In recently analysed clinical material of secondary syphilis followed for two years in major clinics in United Kingdom there was no significant difference in the outcome of the treatment with PAM and bismuth on the one hand and with PAM, arsenicals and bismuth on the other. In a large series of secondary cases in India treated with penicillin and bismuth a similar retreatment rate (12.7 percent) was found as in the British material (13.4%).

Toxic reactions and by-effects

In a recently published investigation covering several years of arsenic-bismuth treatment of syphilis in Denmark (14) *44 percent* of the patients had toxic reactions, 14 of which was not considered to be serious. The reactions included deaths, dermatitis and other recognised toxic manifestations associated with metal-chemotherapy. In a similar material from Britain (15) *14.4 percent* of the patients had serious toxic reactions, including 22 cases of hepatitis. It is inherent in metal-chemotherapy that not only is it difficult to have a high percentage of the patients complete the treatment course because of the relatively long time required, but also the nature of the treatment and its by-effects will deter a certain proportion of the patients from completing the regimen.

In penicillin therapy the classical urticarial response, the erythematous desquamating eruption and the direct contact dermatitis occur most commonly among those who react to the antibiotic. In a large scale study of the frequency of such reactions at the Bellevue Medical Center in New York it was

found that the incidence of reaction between 1947 and 1950 varied from *3.8 to 4.6 percent.* Urticaria was most frequent. The fungus type of response occurred at about one-third of their frequency. Serum-sickness like reactions were comparable in number. The remaining cases were contact dermatoses. The frequency of reactions decreased from 1947 to 1950 in spite of the greatly increased number of patients having been exposed to penicillin therapy over these years.

Relapses and late manifestations

In early infectious syphilis, inadequately treated with arsenicals, a certain proportion of the cases will relapse frankly within the first two years. A proportion will become latent cases, with no other evidence of infection than seropositivity, and these patients are the problem-patients of medical practitioners, venereologists, and clinics in many countries. Other patients will get cardiovascular and neurological involvement late in life, at a time when they represent a medical care problem and when little can be done for them.

One of the outstanding features of penicillin therapy has been the marked reduction in the numbers of relapses other than those in the skin and mucous membranes. Ocular, hepatic, early osseous relapses and neurorecurrences are very rare indeed. Altschuler and his co-workers (16) re-examined 5,590 out of a series of 30,972 patients treated for early infectious syphilis during the recent war with amorphous aqueous penicillin alone, and found cerbrospinal fluid abnormalities only in 0.4 percent of the cases.

In early infectious syphilis, inadequately treated with penicillin the great majority of patients relapse frankly with muco-cutaneous manifestations within the first two years following treatment. Such relapses as well as serological relapses (determined on the basis of quantititive serological tests) occur most frequently between the 9 and the 12 months, very few occuring after the second year. The nature of the muco-cutaneous, frank, clinical relapse is such that it is likely to bring the patient back to clinics or physicians at a time in the life of the patient when he can be successfully retreated. These observations are favourable, but considerably longer periods of time will be required to evaluate completely the long-term ability of penicillin to prevent central nervous system involvement or cardiovascular damage following penicillin therapy, inadequate or adequate.

Prenatal infantile Syphilis

In the treatment of the pregnant woman with syphilis, penicillin is today the treatment of choice. It is, of course, well established that metal-chemotherapy ideally applied is highly efficacious in preventing congenital syphilis. With penicillin the results have been at least equally as good, and there is the additional advantage that adequate amounts can be administered even late in

pregnancy. The greater value of penicillin is to be found not so much in its therapeutic efficacy but in its ease of administration, the lack of serious toxicity and in the shorter period of time necessary to produce the desired results (17).

If untreated, early syphilitic infection associated with pregnancy exacts an enormous toll on unborn children. The probability of a dead or diseased child exceeds four out of five pregnancies. With women whose infection is of longer duration, the chances of fatal infection in the absence of treatment become progressively less as the disease becomes of longer standing.

The results of penicillin therapy in *infantile congenital syphilis* have been even more favourable than those with early syphilis in adults (20). Here again the success of therapy depends on the duration of the infection at the time treatment is instituted. In infants, whose infection was evident at birth or soon thereafter, the results have been excellent. With infections of longer duration, the outlook becomes less bright the longer the infection has been present (Table 1).

Certain of the complications of late congenital syphilis, particularly interstitial keratitis (18) and nerve deafness (19), remain difficult to alleviate completely by any known form of therapy, although it may be stated that as much can be accomplished with penicillin as with prolonged courses of arsenicals and bismuth. Supplementary non-specific treatment with therapeutic malaria frequently is necessary. A late adjuvans in the treatment of interstitial keratitis is cortizon. The excellent effect described appears to merit the attention of the venereologist and the ophtalmologist. (28).

As far as actual treatment schedules are concerned the following considerations have recently been made by a cooperative clinical group with large scale experience in the U. S. A. (29).

In *pre-natal syphilis*, PAM, 600,000 units to be given intramuscularly twice weekly, or 1.2 million units once weekly for four weeks for a total of 4.8 million units. If the patient is in the latter part of pregnancy, a course of shorter duration is frequently desirable. 600,000 of PAM either in oil or aqueous suspension may be given daily for eight days (4.8 million units). If labour is imminent, it is suggested that a single injection of 2.4 million units of PAM be given intra-muscularly and repeated in one week if not delivered. This treatment is to be given for previously untreated or inadequately treated pregnant women in any stage of syphilis. It is aimed primarily at protecting the unborn infant.

In pregnant women who have received adequate treatment with either penicillin or heavy metals need not be retreated if they have progressed to sero-negativity or stabilised as cases of late syphilis which are seroresistant with a low titer. Such cases should be kept under close supervision. If this is not

TABLE I

EARLY AND LATE CONGENITAL SYPHILIS

RESPONSE OF BLOOD SEROLOGIC TEST TO PENICILLIN THERAPY ANALYZED ACCORDING TO AGE WHEN TREATMENT WAS GIVEN (x)

Age when penicillin treatment was given	Total number patients	Blood Serologic Test for Syphilis	Period of Medical Post Treatment Follow-Up in Years								
			At Start Treatment	up to ½	½ to 1	1 to 1½	1½ to 2	2 to 3	3 to 4	4 to 5	More than 5
Before 4 months (median 1-9 months)	57	Per cent Seronegativity attained	0	22	80	98	100	100	100	100	100
4 months to 2 years (median 8-6 months)	23	Per cent Seronegativity attained	0	10	28	25	41	70	38	66	100
More than 2 years (median 16-1 years)	103	Per cent Seronegativity attained	8	11	8	15	13	18	23	25	

(x) Modified from Ingraham.

possible they should be retreated if there is any doubt or any evidence of clinical or serologic relapse. In cases where the need of further treatment is questionable, it is safer to retreat. In such cases, 900,000 units of PAM once weekly for four weeks is suggested.

Penicillin treatment should be given at any time in pregnancy short of actual delivery.

The aim should be to prevent pre-natal syphilis by treatment of the mother during pregnancy. If the presence of syphilis is not discovered until after the fifth month of pregnancy, it may be too late to prevent infection of the fetus, but not too late to offer an excellent chance to cure the baby before birth. If such pre-natal treatment has not been given or has failed, the earlier in infancy the diagnosis can be made and treatment given the better the chance of cure.

The treatment of *congenital syphilis* should be divided into that indicated in early congenital (infants of less than two years of age) and late congenital syphilis.

(a) Early Congenital Syphilis

The following are alternative schedules, depending upon the facilities available and the intervals at which the mother can be expected to report with the baby.

Schedule A: 10,000 units of PAM or aqueous suspension per lb of body weight, given daily for ten days.

Schedule B: 15,000 units of PAM per lb of body weight given twice weekly for four weeks.

Schedule C: 40,000 units of PAM per lb of body weight given once weekly for two treatments.

(b) Late Congenital Syphilis

Ten injections of 2 cc. (600,000 units PAM) for a total of 6 million administered at daily intervals or twice a week for 5 weeks is considered an adequate treatment. These cases are usually serologic fast. As has already been mentioned, in interstitial keratitis, in addition to penicillin (possibly combined with fever therapy) recent reports indicate a local response to the instillation of 2% solution of cortisone into the conjunctival sac.

Implications for other treponemal diseases

Of all the treponematoses, syphilis is the only one in which there frequently is central nervous system or cardiovascular involvement, although these serious late manifestations have been reported as rare complications of yaws (20) and bejel (21).

There is now ample documentation of the fact that penicillin is highly effective in the treatment of all of the clinical manifestations of yaws (2) (22)

(23) (24) (25), bejel (3) and pinta (4), and the inherent safety and easy of administration of penicillin therapy rapidly are bringing it into wider use in many parts of the world.

Implications for mass control programmes

Serum concentrations of penicillin maintained for from 4–10 days suffice to "cure" syphilis (and presumably the other treponematoses as well) in a high proportion of cases, following intramuscular injections (26) of PAM. "Few-shot" schedules of therapy are now within the horizon of practicability and represent a tool in mass campaigns against treponemal diseases.

Schedules feasible for mass application have recently been considered by the Expert Committee on Venereal Infections and Treponematoses of the World Health Organization (27) which has expressed the following opinion :

> "For mass campaigns, it is recognized that penicillin must be conserved insofar as is compatible with effective public health results. There is, however, a limit below which the total dosage of penicillin is not compatible with effective results in a sufficiently high percentage of cases.
>
> "As a compromise between maximum efficacy and practical expediency, it is suggested that field teams consider 1.2 million units of PAM to be the *minimum dosage* for the treatment of early infectious lesions in adults...
>
> "It is further suggested to field teams engaged in mass campaigns that they administer on the day the diagnosis is established the *full minimal total dose* indicated above."

Following this, from the standpoint of field operations, further injections may be given whenever possible, the dosage suggested being one-half that of the first injection at appropriate intervals for total of 2.4 million units.

The World Health Organization and the United Nations International Children's Emergency Fund are presently supporting such large scale campaigns against syphilis in Yugoslavia, and against yaws in Thailand, Indonesia and Haiti. During 1950 more than half a million cases came under penicillin treatment in these countries.

CONCLUSIONS

The availability of modern penicillin preparations has revolutionized the treatment of syphilis and other treponemal diseases, for it has provided the medical profession with a form of therapy that is highly efficacious, almost completely devoid of serious toxicity, and readily administered to ambulatory patients. It has provided health administrations with a means to launch practical mass campaigns against syphilis and other treponemal diseases wherever these conditions are of public health importance.

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Clinical Results and By-Effects in Treatment of Early Syphilis with Combined Arsenical-Bismuth Treatment

By
Povl Miller
(from the University Clinic of Venereology at the National Hospital, Copenhagen, Denmark. Chief Professor H. Haxthausen)

The advantages and disadvantages of penicillin will be briefly summarized here, and the results will be compared with those of combined arsenical-bismuth treatment.

Advantages:

(1) Penicillin is non-toxic.

It may like any other effective antisyphilitic treatment produce a Herxheimer's reaction, but in the early stages of the disease this reaction is of no importance.

(2) Penicillin treatment may be completed in a fraction of the time required for effective treatment with arsenical-bismuth preparations.

Some workers claim to be able to cure early syphilis with a single injection of penicillin.

From an epidemiological point of view it is an immense advantage that the treatment may be concentrated in the shortest possible period, thereby reducing the difficulties in retaining the patients.

Disadvantages:

(1) 10-20 per cent relapses in penicillin treatment are reported. The relapses are stated to be most frequent 3-9 months after treatment, and infrequent after 2 years. Some of the relapses are believed to be reinfections.

(2) A certain number of relapses within the first 2 years will not be ascertained as a large number of patients fail to turn up for control. In the case of clinical relapses, the patients may apply for treatment, but the sero-relapses will remain undetected and may manifest themselves as an outbreak of tertiary syphilis several years later.

(3) Thus far, nothing can be said as to the number of relapses occurring long after the completion of the treatment. No penicillin-treated syphilis patients have as yet been under observation long enough for their final destiny to be ascertained.

Combined arsenical-bismuth treatment:

The appraisal of this treatment is to some extent impeded by the same factors as those which apply to penicillin treatment. As yet, reliable infor-

mation is still missing on the results achieved by successful intensive treatment-particularly with a view to preventing late syphilitic complications. As will be seen below, most of the patients observed for long periods originate from times when it was believed sufficient to administer a small number of salvarsan (arsphenamine) injections.

In Denmark, 551 patients treated in the years 1910–1914 were kept under observation for 3–9 years by Pontoppidan. These patients were given a few salvarsan injections (not exceeding 6) and 50–100 mercurial ointment treatments. In this material he found 22 per cent clinical and 10 per cent serological relapses.

Esbern Lomholt in a more recent material of about 1,800 patients treated between 1920 and 1927, found 5 per cent clinical and 10 per cent serological relapses. Those patients had been treated rather more intensively than Pontoppidan's patients, 3–7 salvarsan injections of 60 or 40 ctgr. having been administered in addition to about 50 mercurial ointment cures and 2–3 series of bismuth injections.

Padget in his carefully examined material from 1939 observed 551 patients through 10 years and found 15 per cent clinical relapses. This high figure is surprizing since the patients were treated at a time when the importance of intensive therapy was realized. However, the explanation must be that the patients did not attend the treatments. (Thus, he reported that the 246 best treated patients received continuous treatment for 6 months, either with arsphenamine, bismuth, mercury, or neosalvarsan " albeit many of them had only a few injections "). Consequently, the intensity of the treatment and the results both conform to Esbern Lomholt's results.

Co-operative clinical group found 9 per cent relapses in 167 patients treated for one year with combined arsenical–bismuth cure. Irregular treatment causes the number of early relapses to increase considerably (E. Thomas).

Garnier found 5 per cent serological relapses in 98 patients observed for 4–19 years. All the relapses were found among patients with secondary syphilis ; there were no relapses at all among patients with primary syphilis. The treatment consisted of 2 series of combined salvarsan–bismuth. His results conform to Moore's statement that a successfully completed arsenical–bismuth treatment results in 95 per cent recovery.

However, the foregoing material represents early clinical or serological relapses.

The question is now : What are the chances for the patients to avoid the late syphilitic complications ?

The answer to this question appears to depend on the course of the early syphilis.

Padget found that in the cases without early relapses the chances of cure were 72 per cent, but the cases involving early relapses the prospects of cure were only 28 per cent. Correspondingly, the incidence of neuro-syphilis was 6 times as high in the patient group with sero-relapses. (36 per cent and 6 per cent).

In a large Swiss material, *Burchardt* found 6.8 per cent late complications in poorly treated patients compared to 0.9 per cent in successfully treated patients with early lues.

The patients in this material were observed for 10–15 years; well-treated patients received 3–4 series (totalling 18–24 grammes) of neosalvarsen and 3–4 grammes of bismuth. He succeeded in carrying out post-treatment examinations of only 20 per cent of the total number of the 475 patients treated.

Among 467 patients treated from 1913 to 1920 and observed through 29–36 years, *Johs. P. Nielsen* found 13 per cent serious late complications. The complications were 4 times as frequent when treatment was begun in the secondary stage as when they were treated in the primary stage.

These patients were treated with 3–6 injections of arsphenamine and with mercury ointments.

Advantages:

Intensive combined salvarsan bismuth treatment at the earliest possible stage will reduce the number of early and late relapses of syphilis to 5 per cent, probably even less.

Disadvantages:

However, there are serious disadvantages in this treatment:

(1) Its by-effects may be so strong that the treatment must be interrupted; in some cases it has even caused death.

According to *Burchardt* neosalvarsen is responsible for vomiting and nausea in 14 per cent of the patient, exanthema in 14 per cent, erythrodermics in 0.9 per cent, icterus in 3.6 per cent, and mors in one half per cent.

Among 5,526 patients *Genner* found 3 per cent with erythema, 2 per cent with icterus, 3 per cent with albuminuria, 1 per cent with arthralgia and subjective by-effects: (nausea, etc.)

(2) The treatment extends over a period which is so long that many patients will fail to complete it.

Inadequate treatment with arsenical-bismuth may be worse than no treatment at all. (Padget; Harrison)

There is hardly any answer which covers all the aspects of the question as to which treatment is preferable.

A combination of arsenical-bismuth and penicillin treatment which reduces the period of the treatment would appear to be advantageous. However, American experiments have resulted in the same number of relapses as the penicillin treatment alone. From the previously reported investigations a limited number of salvarsan injections are known to give comparatively many relapses.

Author's investigations :

I had to confine my investigation to the combined arsenical-bismuth treatment. The objective of the investigation was to find the answers to the following questions :

(1) How frequent are the by-effects of intensive arsenical-bismuth treatment ?

(2) To what extent have the patients been prevailed upon to attend the treatment ?

(3) For how long has it been possible to observe the patients after the completion of the treatment ?

(4) How many relapses and sero-resistant cases are found after this treatment ?

Table No. 1

Distribution by age

Under 20 years	65
20—25 „	207
25—30 „	134
30—40 „	163
Over 40 „	56

Table No. 3

Distribution by disease

Primary syphilis – WR	162
Primary syphilis + WR	143
Secondary syphilis	320

Treatment :

Treatment was intermittent. Treatments were given concurrently for the first 6 weeks, after which bismuth was given alone. In 1944 and 1945 mapharsen was administered instead of neosalvarsan in 177 cases. Effects and by-affects of this arsphenamine substance have not been found essentially different from those of neosalvarsen. There was a pause of 1 to 2 months between the series.

Table No. 2

Schedule of doses

	Men	Women	
Neosalvarsan	gr. 0.75	gr. 0.60	6 times once a week.
Bismuth	„ 0.3	„ 0.25	10 „ „
or			
Mapharsen	„ 0.06	„ 0.04	6 „ „
Bismuth	„ 0.3	„ 0.25	10 „ „

Table No. 3

Series of Treatment

	Number of patients
2 series of treatment	111
3 „ „	325
4 or more series of treatment ...	189

Thus, about 84 per cent have received 3 series of treatment or more. 2 series were mostly given to patients with sero-negative primary lesions whose diseases showed no complications.

Table No. 4

Completion of Treatments

1st group	(0–14 days' delay)	356
2nd „	(½–1 months „)	149
3rd „	(1–5 months „)	36
4th „	(5–8 „ „)	84 (+ 36)

The table shows that more than 50 per cent of the patients attended to the treatment satisfactorily. 76 per cent of the patients (groups 1 and 2) completed their treatment without unreasonable delay.

By-effects:

The intensive and comparatively well-attended treatment is likely to involve a comparatively large number of by-effects. Particularly the bismuth doses were rather large, and consequently caused bismuth-colouration of gingivae in a fairly large number of patients. It may not be quite justifiable to mention this harmless consequence of bismuth treatment among the by-effects. The bismuth treatment was not discontinued in any of the cases ascertained, but the doses were reduced to two-thirds or one-half.

Table No. 5

By effects of combined arsenical bismuth treatment

No by-effects	279	(44%)
Bismuth line	199	(52%)
Bismuth stomatitis ...	85	(13%)
Arthralgia	89	(14%)
Vomiting, nausea	63	(10%)
Albuminuria	15	(2%)
Dermatitis	18	(3%)
Icterus	44	(7%)
Death	1	(0.16%)

Sero-reactions were carried out before the begining of each series of treatments.

Table No 6

Seroreactions consisting of Wassermann, Kahn and Meinicke Reactions

Negative in 0 to 6 months	471	75%
„ „ 6 „ 12 „	101	16%
„ later than 1 year	33	6%
Positive for the entire period of observation	19	3%

Table No. 7

Length of observation

Observation for 0—1 year	55	9%
„ „ 1—2 years	185	30%
„ „ 2—2 years	312	50%
„ „ more than 5 years	73	11%

In conclusion 75 per cent showed no serious by effects. About 25 per cent experienced by-effects sufficient to cause interruption of the treatment, which was later resumed. The treatment caused one death,

76 per cent of the patients attended for treatment satisfactorily (i. e., they completed the course with less than one month's delay).

61 per cent of the cases were followed up by the clinic for periods of two years, and in 13 per cent additional information was received from the Central Registry of Syphilis in Denmark.

19 relapses occured, of which 7 were probably re-infections.

The conclusion is that the arsenical-bismuth treatment of syphilis in a Scandinavian country yields satisfactory results.

2nd All-India Conference of Dermatology & Venereology, Calcutta

An all-India Conference on dermatology and venereology will be held at Calcutta on Saturday, the 14th April and Sunday, the 15th April 1951 under the presidency of Dr. A. C. Rebello of Bombay. Lt. Col. K K. Chatterji & Dr. T. D. Majumdar have been elected as Chairman of the Reception Committee & Hon. General Secretary of the Conference.

The Final programme is as follows :—

Friday, the 13th April, 1951

Morning— Arrival of Delegates.

Evening— Visits to School of Tropical Medicine, All-India Institute of Hygiene & Public Health and other places of interest.

Saturday, the 14th, April, 1951

Morning— Visits to Hospitals.

11-00 a.m. to 1-30 p.m.—Inaugural Session & Selection of Subjects Committee.

1-30 p.m. to 2-30 p.m—Lunch Recess.

3-30 „ to 5-30 „ —Scientific Session.

5-30 „ to 8 00 „ —Exhibition of interesting Cases, Films etc.

8-00 „ —Reception Committee will entertain the members and delegates to a dinner.

After Dinner —Subjects Committee meeting.

Sunday, the 15th, Hpril, 1951

9-00 a.m. to 12 noon —Scientific Session.

12 noon to 2-30 p.m.—Lunch Recess

2-30 p.m. to 4-00 p.m.—Open Session.

It has been decided to charge a fee of Rs. 5/6 only for Conference for Members & Visitors other than delegates.

Delegates from different parts of India have expressed their desire to join and take part in the conference. Papers on scientific and clinical interest will be read. Demonstrations (clinical and microscopic etc.) will be arranged. The committee would be most grateful for any suggestion and would welcome any request. Prior intimations from the delegates, will be much appreciated by the organisers. We appeal to the members of the profession for papers and contributions for the conference.

All Communications should be sent to the Secretary at 15 Camac Street, Calcutta-16, Telephone Number—Park 1540.

WHO Expert Committee on Venereal Diseases

Left: Dr. J. F. Mahoney, Medical Director V. D. Research Laboratory (U.S. Public Health Service), Staten Island, N. Y., U. S. A., Chairman of WHO Expert Committee on Venereal Diseases.

Right: Dr. T. Guthe, Chief of the Venereal Diseases Section at W. H. O. Geneva Head quarters who arrived at Bombay in February this year had a busy time visiting various Institutions, delivering lectures and contacting several persons interested in V. D. The Association of Dermatologists and Venereologists, Bombay invited him to a dinner, arranged a lecture under its auspicious. Dr. Guthe, after visiting important cities in India on a three month's tour of S. E. Asian countries before he goes back to Geneva.

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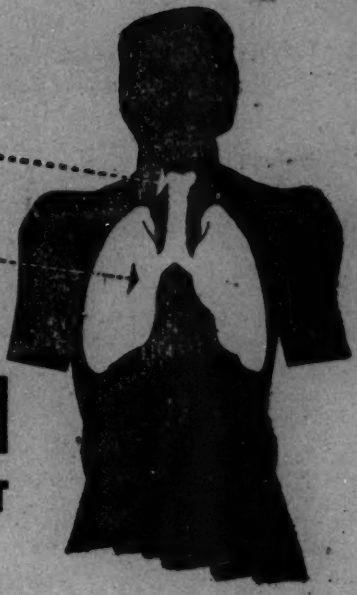

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